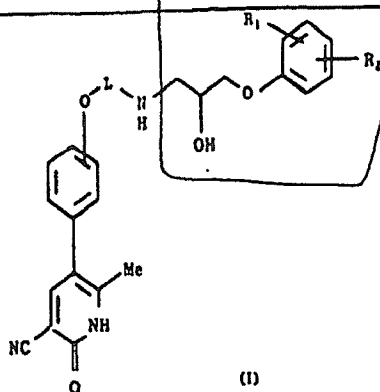


91-088869/13 803 GLAX 22.09.89
GLAXO INC *EP 419-286-A
09.08.90-US-565297 (+US-411065) (27.03.91) A61k-31/43
C07d-213/85
New phenoxyl-substit. pyridone nitrile(s) - are used in treating
cardiovascular disease, esp. congestive heart failure
C91-037751 R(AT BE CH DE DK ES FR GB GR IT LI LU NL SE)

Pyridone derivs. of formula (I) and their acid addn. salts
are new:

B(7-D4C, 12-F1C)



$R_1, R_2 = H, \text{ lower alkyl, morpholino, CN, halo, CF}_3,$

EP-419286-A+

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alkyl (opt. substd. by alkoxy or cycloalkylalkoxy),
alkylsulphonyl, NO_2 , OH, alkenyloxy, NH_2 or mono-
or di-alkylamino;

$L = (\text{CR}_1\text{R}_2)_n \text{CON}(\text{R}_3)\text{CR}_4\text{R}_5\text{R}_6$ (gp. (a)) or
 $(\text{CR}_{10}\text{R}_{11})_p$;

$R_1 - R_{11} = \text{independently H or lower alkyl};$

$n = 1-3;$

$p = 2-6.$

MORE SPECIFICALLY

$L = \{a; n = 1-3\}$ or $\{b; p = 3\}$ and OL is at the 4-position.

$R_1 - R_9, R_{10}$ and $R_{11} = H;$

R_8 and $R_9 = H$ or Me;

either

(1) $R_1 = H;$

$R_2 = \text{CN, Cl or Me};$

(2) $R_1 = H;$

$R_2 = H, \text{ CN or Cl};$ or

(3) $R_1 = H$ or Cl;

$R_2 = H, \text{ CN or Cl at the 2-position.}$

USE

(I) are positive inotropic and β -adrenergic agents useful
for treating congestive heart failure. Dose is 0.1-5 $\mu\text{g/kg}$ 1-4
times a day.

SPECIFICALLY CLAIMED

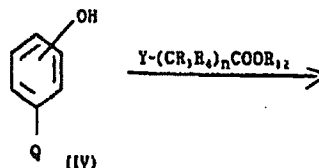
13 Cpts. (I) e.g. 5-(4-(N-(2-(3-phenoxyl-2-hydroxy-
propylamino)ethyl)carbamoylmethoxy)phenyl)-6-methyl-2-
oxo-1,2-dihydro-3-pyridinecarbonitrile (Ia);
5-(4-(N-(2-(3-(2-cyanophenoxy)-2S-hydroxypropylamino)-
2-methylpropyl)carbamoylpropoxy)phenyl)-6-methyl-2-oxo-
1,2-dihydro-3-pyridinecarbonitrile; and
5-(4-(N-(2-(3-(2-chlorophenoxy)-2S-hydroxypropylamino)-
2-methylpropyl)carbamoylmethoxy)phenyl)-6-methyl-2-oxo-
1,2-dihydro-3-pyridinecarbonitrile.

WIDER DISCLOSURE

Intermediates of formula (VI), (VII), (X), (XVII) and
(XVIII) are stated to form part of the invention.

PREPARATION

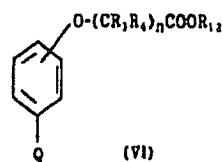
(I)



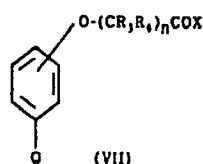
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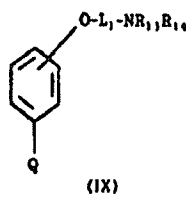
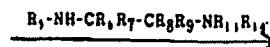
91-088869/13



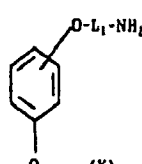
(VI)



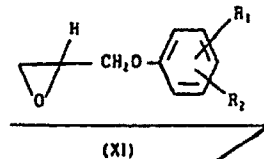
(VII)



(IX)



(X)



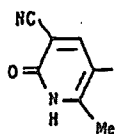
(XI)

(I; L=(a))

EP-419286-A+/2

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Q =



X = leaving gp. (e.g. OH);

Y = leaving gp.;

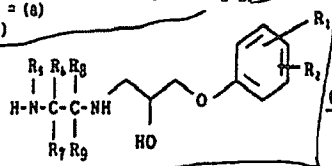
R₁ = H;

R₁ = amino protecting gp.;

or R₁ + R₁ = amino protecting gp.;

L₁ = (a)

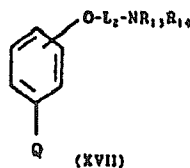
(II)



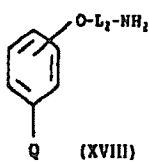
(VII) → (I; L(a))

(III)

(IV) Y-(CR₁₀R₁₁)_pNR₁₂R₁₃



(XVII)



(XVIII)

(XI) → (I; L = (b))

L₂ = (b)

EXAMPLE

A soln. of 500 mg 5-(4-carboxymethoxyphenyl)-6-methyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile, 407 mg (±)-

EP-419285-A/3

91-088889/13

-N-(2-aminoethyl)-2-hydroxy-3-phenoxypropylamine and 316 mg diethyl cyanophosphonate in 10 ml DMF is cooled (ice bath) and treated dropwise with 540 µl Et₃N in 2 ml DMF. The mixt. is allowed to slowly warm to room temp., stirred overnight under N₂ then evapd. in vacuo. The residue is chromatographed over silica gel, eluting with CHCl₃/MeOH/NH₄OH (90:10:2). The solid is recrystd. from EtOAc/MeOH to give 185 mg (21%) (1a), m.pt. 136-138°C. (29pp985HBDwgNo0/0)

(E) ISR: No Search Report.

EP-419285-A/4